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TRICHLOROETHYL ESTERS AS DERIVATIVES FOR GAS CHROMATOGRAPHY WITH ELECTRON CAPTURE DETECTION

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SUMMARY

Esters of 2,2,2-trichloroethanol were studied as derivatives for gas chromatography with electron capture detection. The ester derivatives of ten model benzenoid carboxylic acids were prepared and characterized. Good gas chromatographic development of these compounds was observed and their separation was achieved on a 3% OV-17 column. A rapid and quantitative esterification technique was developed for small scale preparation based on reaction with 2,2,2-trichloroethanol in trifluoroacetic anhydride. The trichloroethyl esters were found to be sensitively measured with a nickel-63 electron capture detector.

INTRODUCTION

Gas chromatography combined with electron capture detection (GC/EC) provides the most sensitive method of analysis for certain organic compounds. The particular utility of GC/EC in the assay of many halogen-, phosphorus-, and sulfur-containing pesticides is well documented[1–5]. The sensitivity of the EC detector, however, is limited to relatively few types of materials.

One of the most intriguing applications of GC/EC has been its use with selected derivatives of compounds which would otherwise be unsuitable for EC detection. Of these, derivatives containing halogens (especially those substituted on sp^3-carbon atoms) seem to be most important from the standpoint of sensitivity. Derivatives for the GC/EC of carboxylic acids have been sought in the last few years. Bromo- and chloromethyldimethylsilyl esters have been prepared for this purpose[6], however, they suffer the disadvantage of being prone to facile hydrolysis[7]. KAWAHARA[8] made pentafluorobenzyl esters for GC/EC but the derivatization method employed appears cumbersome and requires the use of a strong lachrymator. The preparation of 2-chloroethyl esters[9] of certain herbicidal acids has been reported though application of these to the GC/EC method or details of this work have not been published.

It was proposed that a study be undertaken to determine the utility of esters of 2,2,2-trichloroethanol in the GC/EC technique. Because of their potentially high electron affinity[10–12], it was anticipated that they would be sensitivily measured by EC detection. The preparation and gas chromatographic properties of the trichloroethyl esters of ten model benzenoid acids are presented in this report.

TABLE I

2,2-TRICHLOROETHYL ESTERS

Compound		*b.p./m.p.* (°C)	*Elemental analysis*			*Yield*[a] (%)		*Retention time* (*min*)[b] (*column temp.*)	*IR*[c] ($\nu C = O$) (cm^{-1})
No.	*Ester of*			*Calc.*	*Found*	*Preparative*	*Analytical*		
1	Benzoic acid	111–112[d] (10 mm)	C H Cl	42.60 2.76 42.01	42.71 2.94 42.19	93.1	>98	3.0 (180)	1731
2	*p*-Methoxybenzoic acid	46–47[e]	C H Cl	42.31 3.17 37.57	42.51 3.20 37.45	90.0	>98	2.7 (220)	1725
3	3,4-Dimethoxybenzoic acid	102–103	C H	42.11 3.51	41.79 3.59	77.0	>98	5.2 (220)	1727
4	3,4,5-Trimethoxy-benzoic acid	88–89	C H	41.86 3.78	41.97 4.00	73.6	>98	7.4 (220)	1727
5	Phenylacetic acid	121–122 (2 mm)	C H Cl	44.86 3.36 39.81	44.88 3.37 39.81	95.3	>98	4.2 (180)	1750
6	3,4-Dimethoxy-phenylacetic acid	160–162 (0.2 mm)	C H Cl	43.97 3.97 32.52	44.15 4.09 32.20	88.2	>98	6.4 (220)	1754
7	Hippuric acid	127–128	C H N	42.54 3.25 4.51	42.66 3.39 4.35	74.8	<10	11.2 (220)	1765 1666
8	*p*-Nitrobenzoic acid	67–69[f]	C H N	36.18 2.01 4.69	35.82 2.06 4.73	90.0	<10	3.8 (220)	1739
9	*trans*-Cinnamic acid	178–180 (4.2 mm)	C H Cl	47.23 3.22 38.10	47.46 3.38 37.82	79.2	>98	2.5 (220)	1719
10	Bis(*p*-chlorophenyl) acetic acid	79–80	C H Cl	46.55 2.67 43.03	46.49 2.64 43.08	91.1	>98	9.8 (250)	1752

[a] See EXPERIMENTAL for conditions.
[b] Relative to solvent front.
[c] In chloroform.
[d] Ref. 14, b.p. 106–107° (1 mm).
[e] Ref. 15, m.p. 46°.
[f] Ref. 16, m.p. 69–70°.

EXPERIMENTAL

Materials

The following carboxylic acids were employed: benzoic, Fisher (reagent grade); *p*-methoxybenzoic, Aldrich (98 %); 3,4-dimethoxybenzoic, Aldrich (99+ %); 3,4,5-trimethoxybenzoic, Aldrich (99 %); phenylacetic, Aldrich (98.5 %); 3,4-dimethoxyphenylacetic, Aldrich (99 %); hippuric, Matheson (recrystallized from ethanol); *p*-nitrobenzoic (prepared by alkaline hydrolysis of *p*-nitrobenzoyl chloride; recrystallized from ethanol); *trans*-cinnamic, Aldrich (99+ %); bis(*p*-chlorophenyl)acetic, Aldrich (99 %).

2,2,2-Trichloroethanol, Aldrich, was redistilled. All other reagents and solvents were reagent grade.

Preparative synthesis of trichloroethyl esters. A mixture of carboxylic acid (0.01 mole), 2,2,2-trichloroethanol (0.10 mole), sulfuric acid (0.2 g), and benzene (100–150 ml) was refluxed for 48 h; water was collected in a Dean-Stark trap. The cooled reaction mixture was extracted with 5 % sodium bicarbonate, washed with water, and dried over anhydrous sodium sulfate. After reduction to dryness *in vacuo*, the residue was recrystallized from ethanol or distilled at reduced pressure. Yields and characterizing data are given in Table I.

Small scale synthesis of trichloroethyl esters. Carboxylic acids (10 mg) were reacted for 10 min on a steam bath with 10 % 2,2,2-trichloroethanol in trifluoroacetic anhydride (1 ml). With flame ionization detection, the reaction mixtures were diluted with ethyl acetate or *n*-heptane prior to injection; yields are indicated in Table I. For EC detection, the trifluoroacetic anhydride was evaporated under a stream of dry air. The residual trichloroethanol was removed by preparing a solution in ethyl acetate (100 ml) and passing the latter over a short silica gel column (20 g). The effluent was diluted with ethyl acetate or *n*-heptane for subsequent GC/EC.

Reference solutions

Reference trichloroethyl esters were submitted to GC as solutions in *n*-heptane or ethyl acetate.

Gas chromatography

A Hewlett-Packard 5750B gas chromatograph equipped with flame ionization and nickel-63 EC detectors was used throughout. The column employed in all studies was a 6 ft. × 1/4 in. I.D. glass column packed with 3 % OV-17 on 100–120 mesh Gas-Chrom Q; packing and conditioning were according to DE FAUBERT MAUNDER *et al.*[13].

Flame ionization detection. The following conditions were used: injection port temperatures, 225° for compounds 1–9, 250° for compound 10; column temperatures, as indicated in Table I; detector temperature, 275°; carrier gas (He) flow, 120 ml/min (50 p.s.i.g.); hydrogen flow, 40 ml/min (13 p.s.i.g.); air flow, 440 ml/min (30 p.s.i.g.); range, 10^3; attenuation, 16.

Nickel-63 EC detection. Temperature control was as indicated under flame ionization detection, except the detector temperature, which was maintained at 230° (for compounds 1–9) or 260° (for compound 10). Other conditions were: carrier gas (Ar–CH_4, 95:5) flow, 120 ml/min; purge (Ar–CH_4, 95:5) flow, 30 ml/min; range, 10^2; attenuation, 8; pulse interval, 50 µsec.

RESULTS AND DISCUSSION

Preparative synthesis of trichloroethyl esters

Initially, attempts to preparatively synthesize trichloroethyl esters were with the method of KUHN AND CORWIN[14]. Optimum yields, however, were only achieved when sulfuric acid was substituted as catalyst and the molar ratio of alcohol to carboxylic acid was increased to 10:1.

Gas chromatographic development

Suitability of the trichloroethyl esters for GC was investigated. Preliminary experiments with copper columns revealed significant decomposition. This problem was generally obviated by use of a glass column. The chromatographic characteristics and separation of esters 1–10 are shown in Fig. 1. With isothermal and programmed-temperature development, symmetrical peaks were observed for all derivatives except that of hippuric acid (compound 7). In addition to its poor development, it was suspected that this particular compound undergoes decomposition since detector responses to it were consistently lower than those of the other derivatives.

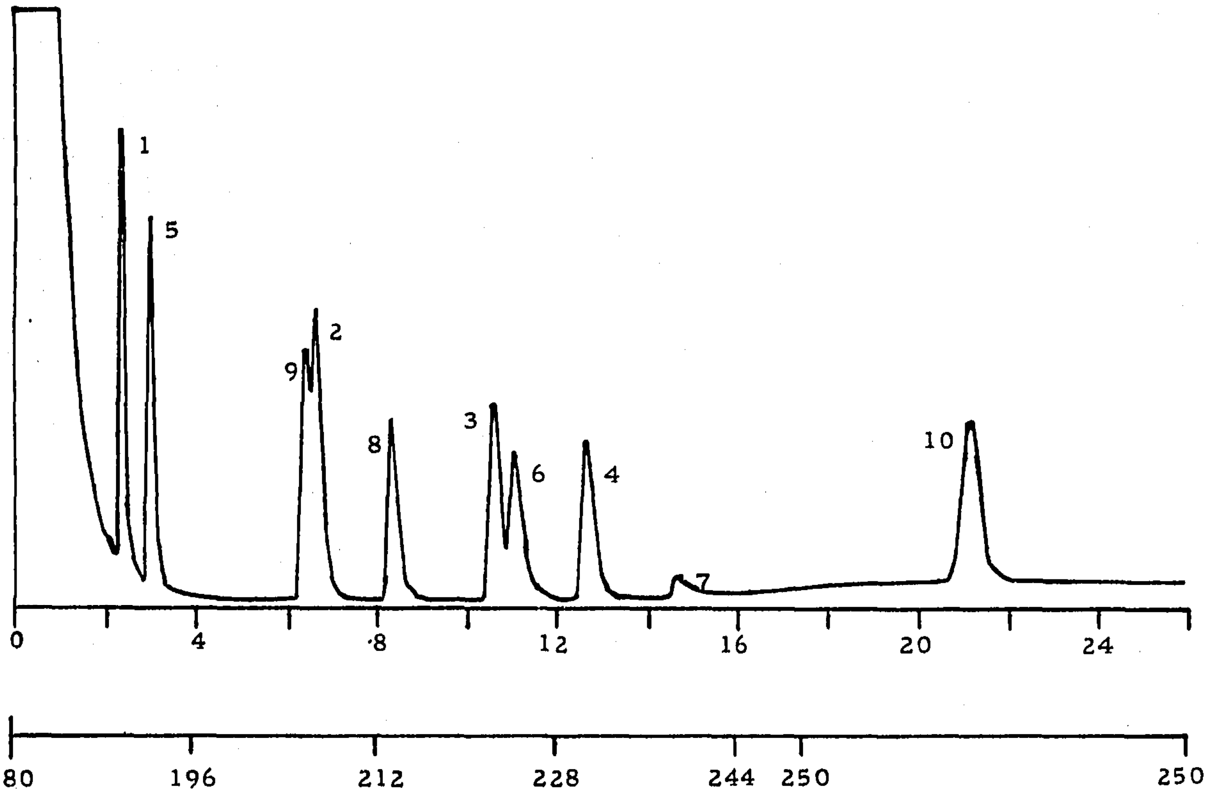

Fig. 1. Separation of the trichloroethyl esters of (1) benzoic acid, (2) *p*-methoxybenzoic acid, (3) 3,4-dimethoxybenzoic acid, (4) 3,4,5-trimethoxybenzoic acid, (5) phenylacetic acid, (6) 3,4-dimethoxyphenylacetic acid, (7) hippuric acid, (8) *p*-nitrobenzoic acid, (9) *trans*-cinnamic acid, and (10) bis(*p*-chlorophenyl)acetic acid on a 6 ft. × 1/4 in. 3% OV-17 on Gas-Chrom Q column; temperature programmed, 4°/min from solvent front up to 250° and held.

Analytical preparation of trichloroethyl esters

Methods were sought which would provide rapid and quantitative esterification. Various catalysts were tried including boron trifluoride-etherate[17] (10 % in trichloroethanol), acetyl chloride[18] (20 % in trichloroethanol), boron tribromide (10 % in trichloroethanol), and trichloromethanesulfonyl chloride (10 % in trichloroethanol). In all instances, solutions were reacted at varying intervals: first, at room temperature and then heated at temperatures up to reflux. The extent of derivatization was monitored by GC. None of the reagents noted resulted in yields greater than 30 %.

A recent review of functional group reactions[19] led to the studies of PARISH AND STOCK[20] on the use of trifluoroacetic anhydride in esterifications. Various combinations of trifluoroacetic anhydride and trichloroethanol were tried for preparation of trichloroethyl esters. Excellent and equivalent results were obtained with 10–50 % trichloroethanol in trifluoroacetic anhydride; a combination of 10 % trichloroethanol in trifluoroacetic anhydride was adopted for routine use since the latter reagent was easier to eliminate following reaction. While the reactions were relatively slow at room temperature, quantitative derivatization was observed for eight of the ten acids after ten minutes' heating on a steam bath (see Table I). The low yield with hippuric acid may be due to competitive formation of 2-phenyl-5-oxazolone, which is reported to form with acetic anhydride[21]. The poor yield with *p*-nitrobenzoic acid may be due to anhydride formation, which results from ring deactivation by the nitro-function[20].

Since EC detectors are easily fouled by halogenated solvents/reagents, a means of eliminating excess trifluoroacetic anhydride and trichloroethanol was required. This was readily accomplished by air-evaporating the former and removing the trichloroethanol by passage over a short silica gel column. Following the latter treatment, no trichloroethanol could be detected by GC.

EC detection of trichloroethyl esters

Most of the derivatives prepared were sensitively detected by nickel-63 EC detection as indicated in Table II. For all compounds except 7, linear curves (peak

TABLE II

NICKEL-63 ELECTRON CAPTURE DETECTION OF 2,2,2-TRICHLOROETHYL ESTERS

Compound No.	*Detector response*[a] *(peak height)*		*Detection limit (ng)*[b]
	(mm/ng)	*(mm/pmole)*	
1	12.5	3.17	0.08
2	3.3	0.94	0.30
3	2.0	0.63	0.50
4	1.8	0.62	0.56
5	3.9	1.04	0.26
6	1.0	0.32	1.00
7[c]	—	—	—
8	5.4	1.61	0.19
9	2.5	0.70	0.40
10[d]	0.6	0.25	1.70

[a] Attenuation, 10^2; range, 8; pulse interval, 50 μsec; detector temperature, 230°; carrier flow, 120 ml/min; purge, 30 ml/min; column temperature, see Table I.

[b] Amount of compound giving two times the noise level.

[c] Showed no response up to 10 ng; apparently due to decomposition on column.

[d] Detector temperature, 260°.

height or disc integration *vs.* amount chromatographed) were produced in the range 2 to 10 ng. The detection limits are with instrumental conditions yielding very low noise levels (equivalent to pen deflections of 0.5 mm or less). Since the various derivatives were developed at different column temperatures and some possessed different peak characteristics, extensive deductions from the data in Table II regarding relative electron capture affinities may not be valid. However, it seems reasonable to note that the relatively close detection responses for these compounds suggest a common capture mechanism, most likely based on the trichloromethyl group of the common ester function.

Because of their favorable GC/EC properties, trichloroethyl esters should have value in the analysis of minute amounts of carboxylic acids in biological fluids. Their application to a number of biomedical problems is currently being pursued in these laboratories.

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